DR. ALDO J. MONTANO-LOZA (Orcid ID : 0000-0002-2511-7980)

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RECURRENT AND DE NOVO AUTOIMMUNE HEPATITIS

Guido Stirnimann, MD.[1]

Maryam Ebadi, PhD.[2]

Albert J. Czaja, MD.[3] *

Aldo J. Montano-Loza, MD; PhD.[2] *

*Denotes co-senior authors

Running title: Autoimmune hepatitis after liver transplant

From the [1]Department of Visceral Surgery and Medicine, Inselspital Bern, Bern University Hospital and University of Bern, Bern, Switzerland; [2]Division of Gastroenterology & Liver Unit, University of Alberta Hospital, Edmonton, Alberta, Canada; and [3]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota USA;

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Abbreviations:

AIH	autoimmune hepatitis
anti-LKM1	antibodies to liver-kidney microsome type 1
ANA	antinuclear antibodies
HLAs	human leukocyte antigens
IgG	immunoglobulin G
GSTT1	glutathione-S-transferase T1
LT	liver transplantation
PBC	primary biliary cholangitis
*r*AIH	recurrent AIH
SMA	smooth muscle antibodies

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Corresponding author:

Aldo J. Montano-Loza, MD, PhD

Associate Professor of Medicine

Division of Gastroenterology and Liver Unit

8540 112 Street NW,

Zeidler Ledcor Centre, Room 1-20B

Edmonton, AB, T6G 2X8, Canada

Tel (780) 248-1892

Fax (780) 248-1895

Email: montanol@ualberta.ca

ABSTRACT

Clinical indications for liver transplantation (LT) in patients with autoimmune hepatitis (AIH) are identical to those of patients with other chronic liver diseases that end in acute or semi-acute liver failure, decompensated cirrhosis, or hepatocellular carcinoma. Recurrent disease after LT has been reported in 10-50% of patients with AIH, and the frequency of detection is influenced in part by the use of protocol or clinically indicated liver biopsy. D*e novo* AIH connotes the development of AIH in patients transplanted for liver diseases other than AIH, and it has been reported in 5-10% of pediatric and 1-2% of adult recipients. Recurrent disease can negatively impact on graft and patient survival, and re-transplantation has been required in 8-23%. *De novo* AIH is within the spectrum of graft dysfunction that includes plasma cell-rich rejection, and it can also progress to cirrhosis and graft failure. Treatment for recurrent or *de novo* disease is based on the conventional regimens for AIH, and corticosteroid therapy alone or combined with azathioprine is standard. Better control of disease activity prior to LT has been associated with less recurrence, and maintenance corticosteroid treatment after LT can reduce its frequency. **Conclusions.** Recurrent AIH is far more frequent than *de novo* AIH. Both may have negative impacts on graft and patient survival, and early detection and treatment are key objectives. Future investigations must codify the diagnostic criteria for each graft dysfunction, seek diagnostic biomarkers, and evaluate treatments that improve outcomes without increasing the risk of pre- and post-LT infections.

INTRODUCTION

Autoimmune hepatitis (AIH) is a complex and rare disease, characterized by hypergammaglobulinaemia, autoantibodies, certain human leukocyte antigens (HLAs), interface hepatitis on histological examination, and in most cases, an appropriate response to

immunosuppression (1, 2). Its clinical, laboratory, immunological and histological features are diverse, and the diagnosis should be considered in all patients with acute or chronic liver disease, particularly if hypergammaglobulinemia and other autoimmune diseases are present.

Clinical indications for liver transplantation (LT) in patients with AIH are identical to patients with other chronic liver diseases that end in acute or semi-acute liver failure, decompensated cirrhosis, or hepatocellular carcinoma (3). Liver transplantation has been a lifesaving intervention for decompensated AIH, and 1- and 5-year survivals are approximately 90% and 70%, respectively (4). Recurrent AIH (*r*AIH) is a cause of allograft dysfunction, reduced graft and patient survival, and need for re-transplantation. Its prevalence increases with time after LT, and prompt diagnosis and intervention are essential in preventing or limiting its consequences.

The prevalence of *r*AIH ranges from 17-42% (5-7), depending in part on the use of protocol liver biopsy assessments or a clinically indicated liver biopsy strategy. Quality of life as well as graft and patient survival may be adversely affected by *r*AIH regardless of the immunosuppression regimens employed (8, 9). Diagnosis is challenged by the variable criteria used to define disease recurrence, the lack of specific biomarkers for *r*AIH, and the difficulty in distinguishing *r*AIH on histological examination from alloreactivity. Acute and late onset T-cell mediated rejection (occurring after 90 days) develops more frequently in recipients with AIH than recipients with other liver diseases, and this may confound the clinical and histological diagnosis of *r*AIH (3, 10).

De novo AIH develops in recipients transplanted for other reasons than AIH. This condition was initially described in children after LT, predominantly in patients with biliary atresia (11). Subsequently, *de novo* AIH has been recognized in adults transplanted for other etiologies, and one series reported a higher prevalence in recipients with primary biliary cholangitis (PBC) (12). The incidence of *de novo* AIH is unknown as the disease lacks

codified diagnostic criteria. Furthermore, the outcome of *de novo* AIH is unclear as studies assessing its impact on graft or patient survival are small. Recipients of female grafts or older donors have a higher prevalence of *de novo* AIH, suggesting that the risk associated with *de novo* AIH may be dictated by the allograft itself (12).

Published literature uses highly variable diagnostic criteria, different regimens of maintenance immunosuppression and relies heavily on biopsy features, none of which are specific for AIH. Thus, in the absence of both validated diagnostic biomarkers for AIH or validated diagnostic criteria for either *r*AIH or *de novo* AIH post-LT, we have critically evaluated the published literature in this review. We describe the frequency and risk factors associated with the development of recurrent and *de novo* AIH following LT. We also discuss the clinical significance and management strategies for each of these graft dysfunctions.

Autoimmune Hepatitis

AIH is a chronic inflammation of the liver associated with interface hepatitis, increased serum immunoglobulin G (IgG) level, and autoantibodies (1, 13, 14). The pathogenesis is not completely understood, but AIH is probably triggered by environmental elements in a genetically susceptible individual. Patients develop loss of self-tolerance, and dysregulated T-cell mediated immune responses can result in long-term hepatic inflammation, injury, and fibrosis (15).

Two types of AIH (type 1 and type 2) are recognized based on serological markers (2, 16). Type 1 AIH is characterized by the presence of antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or both, and it constitutes more than 80% of cases. Type 2 AIH is characterized by antibodies to liver-kidney microsome type 1 (anti-LKM1) and/or antibodies to liver cytosol antigen type 1 (anti-LC1). Most patients with type 2 AIH are children (14). Type 3 AIH was described after the finding of antibodies against soluble liver antigens (anti-

SLA) (17). These antibodies were subsequently found to have identical reactivities to the previously described antibodies against liver pancreas (anti-LP) (18), and the early designation of these antibodies as anti-SLA/LP indicated this identity (19). The subclassification of type 3 AIH is still controversial as the difference in clinical behaviour between type 1 and type 3 AIH is not significant (2).

Liver Transplantation for AIH

AIH accounts for approximately 6% of all pediatric and adult LTs in North America (16). Patients with AIH that need a LT can present with either acute liver failure with poor response to treatment, decompensated cirrhosis at diagnosis or after prolonged immunosuppression therapy, or less frequently, with hepatocellular carcinoma (20, 21). Factors predictive of treatment failure and disease progression are young age at diagnosis, acute presentation, high serum bilirubin level, MELD score >12 at diagnosis, and the HLA DRB1*03 phenotype (20). It has been reported that lack of response to standard immunosuppressive regimens is predictive of LT, especially when there is less than 50% improvement of serum aminotransferase levels after 6 months of treatment (22). In general, outcomes after LT for patients with AIH are satisfactory, with a 5- and 10-year overall survival of 86% and 73%, respectively (Table 1) (23).

Possible Pathogenic Pathways for *r*AIH and *De novo* AIH

The pathogenic mechanisms for AIH before LT are probably similar to those that promote recurrent and *de novo* AIH, but the introduction of a donor allograft with different antigen-presenting and immune-reactive cells can alter the recipient's immune response. Autoimmunity infers that there is a loss of tolerance for self-antigens and that an immune response is mounted against host antigens presented by host-derived antigen-presenting cells

(24). After LT, autoantigens may not only be presented by self-derived class I and II HLA and recognized by self-derived CD4+ and CD8+ T cells, but they may also be presented by donor-derived HLA. Recipient memory T cells that should be restricted to self-derived HLA may also react with donor-derived HLA, and *r*AIH may be a consequence. In *de novo* AIH, there has been no preceding autoimmune reaction in the recipient, and the donor liver may introduce new antigens and immune-reactive cells that institute a weakening of immune tolerance (25).

A similar mechanism has been observed in patients with hepatitis C virus (HCV) infection following LT. HCV-specific CD8+ T cells have recognized viral antigen presented by HLA-A2 in the allograft in a HLA-A2 negative recipient, *i.e.* by non-self HLA on donor hepatocytes (26). The genetic susceptibility provided by HLA DRB1*0301 and DRB1*0401 alleles has been associated with *r*AIH (27), but the role of the HLA phenotype in *de novo* AIH is not certain. It is speculated that presentation of antigens by the donor or recipient antigen-presenting cells activates the memory T cells of the recipient, which in turn enables a self-directed immune attack (28) (Figure 1).

Hidden or sequestered epitopes may also contribute to immune-mediated graft damage as inflammation and tissue injury can trigger reactive T cells that unmask neo-antigens (29). Furthermore, reactivity to an immunodominant epitope may expand to neighboring and remote regions of the epitope in association with the disease duration. The expansion of reactivity to sequence homologies within the same antigen constitutes an epitope spread, and it supports molecular mimicry as a possible mechanism of autoreactivity after LT (30). Viral infection has been proposed as a trigger for *r*AIH and *de novo* AIH, but this finding requires corroboration (31).

Most cases of *r*AIH and *de novo* AIH occur in patients receiving calcineurin inhibitors (CNI). CNI obstruct T cell activation through T cell receptors, where interleukin-2 (IL-2) is required for the survival and proliferation of regulatory T cells (Treg). As CNI decrease the production of IL-2, Treg function may be altered. In animal models, autoimmune disease caused by CNI has been related to impairment of T cell-regulated suppressor function and subsequent development and activation of auto-reactive T cells (32, 33).

The triggering antigens in post-LT AIH may differ, and the alloreactive responses may be modified by ongoing antirejection treatment. Patients developing *r*AIH have already demonstrated a defect in immune tolerance for auto-antigens, and the factors that predisposed individuals to develop the original disease are unlikely to change after LT. In patients with *de novo* AIH, exposure of the recipient to new antigens and immune cells from the graft, re-population of the donor liver with antigen-presenting cells from the recipient, sequestration and re-activation of antigen-sensitized lymphocytes within the recipient, and drug-induced alterations in immune regulatory cells could promote autoreactivity (Figure 1) (34).

Recurrent Autoimmune Hepatitis

Frequency of rAIH

Establishing an accurate estimate of frequency for *r*AIH has been difficult. Different groups have employed diverse diagnostic criteria and strategies for sampling liver tissue (5). The diagnostic criteria for *r*AIH have not been codified by the International Autoimmune Hepatitis Group (IAIHG) or other liver societies (35), and the diagnostic scoring systems for AIH have not been validated for *r*AIH (36). Furthermore, the histological features of *r*AIH may be atypical of classical AIH, and the manifestations of focal lymphocytic cholangitis and

perivenular hepatocyte necrosis of the terminal hepatic venules may suggest T-cell mediated rejection (37, 38). The diagnosis of *r*AIH cannot be made by histological examination alone, and the required clinical and laboratory features that support the diagnosis lack diagnostic specificity. Consequently, it is not surprising that the reported frequency of *r*AIH ranges from 10-68% depending on the diagnostic criteria that are applied and on the observation interval after LT. The frequency of *r*AIH increases with time after transplantation, and *r*AIH has been found in 8-12% after 1 year (39, 40) and 36-68% after 5 years (5, 39).

Case series have been too small to demonstrate an increased risk of graft loss or mortality in recipients with *r*AIH compared to recipients with other liver diseases. Nevertheless, progression to cirrhosis, graft failure, and re-transplantation have occurred with *r*AIH (41, 42), and these possible outcomes, estimated at 13-23% in small series, have justified efforts for early diagnosis and effective treatment.

Diagnostic Features of rAIH (Table 2)

The diagnostic criteria for *r*AIH are the same that have been promulgated for the original disease (16, 35). Post-transplant variations in the clinical phenotype of *r*AIH can complicate its recognition, and some features may be less pronounced, absent, or otherwise atypical in part because of concurrent antirejection therapy and the duration or stage of the disease before its detection (43-45). Patients may be asymptomatic, and the diagnosis considered only because surveillance tests reveal serum aminotransferase abnormalities and the need for liver tissue examination. Other patients may have normal liver tests but abnormal protocol-directed liver tissue examinations (43, 44). An acute severe hepatitis is a rare possibility because of concurrent immunosuppressive therapy.

Interface hepatitis is the hallmark of *r*AIH with or without plasma cell infiltration (37, 46). Primary histological alterations include acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells, and pseudo-rosetting of hepatocytes

(37, 46). Delayed histological alterations are lymphoplasmacytic portal and lobular infiltrates and interface hepatitis (37). Confluent and bridging necrosis with lymphoplasmacytic infiltration connote severe inflammatory activity.

All causes of allograft dysfunction in patients transplanted for AIH must be considered as *r*AIH, and the diagnosis requires the exclusion of other considerations, especially allograft rejection. Drug hepatotoxicity, *de novo* steatohepatitis, and viral hepatitis, including hepatitis E, should be excluded.

The presence of focal lymphocytic cholangitis and perivenular hepatocyte necrosis of the terminal hepatic venules support the possibility of T-cell mediated rejection (37). Main histological aspects of *r*AIH are prominent lymphocytic interface activity, pseudo-rosetting of hepatocytes, and perivenular lymphoplasmacytic inflammation (37).

Risk Factors for rAIH (Table 3)

The risk factors for *r*AIH after LT are poorly understood. Inflammatory activity prior to LT has been associated with *r*AIH (5). Increased serum aminotransferase and IgG levels prior to LT as well as the presence of lymphocytic or lymphoplasmacytic infiltration with moderate to severe inflammatory activity in the explant have been associated with a high risk of *r*AIH (5). Furthermore, HLA DRB1*03 has been associated with severe AIH before LT and *r*AIH after LT (27, 47). These results suggest that active disease before LT directly impacts on the development of *r*AIH and that recurrence may simply be a continuum of the original disease (34, 48). Future studies must evaluate if more powerful immunosuppression prior to LT can reduce the occurrence of *r*AIH. They must also determine if the benefit can counterbalance the increased risk of side effects from more intense pre-operative therapy.

Other risk factors that have been proposed but remain unestablished are HLA mismatching between donor and recipient (47), antecedent episodes of rejection (49), corticosteroid withdrawal and inadequate immunosuppression (50), and a paradoxical

stimulatory immune response induced by the calcineurin inhibitor (51). When HLA DRB1*03 mismatching was evaluated in one case series, the frequency of mismatching did not have any impact on the frequency of *r*AIH (52). In contrast, HLA mismatching at the DR locus was associated with an increased frequency of *r*AIH in the National Institutes of Health Liver Transplantation Database. HLA mismatching, however, did not predict patient or graft survival (53), and no changes in current management guidelines were recommended.

The development of T-cell mediated rejection did not influence the frequency of *r*AIH (3); and experiences evaluating the association of low dose maintenance immunosuppression and corticosteroid withdrawal with the risk of *r*AIH (40, 52) have been discrepant (39, 54). Firm conclusions about the impact of corticosteroid withdrawal in AIH post-LT cannot be made from these uncontrolled studies, but the maintenance of long-term, low dose corticosteroid therapy after LT has generally been well tolerated and mitigates concern about *r*AIH. This approach has been supported by the findings in a British study that has demonstrated the safety of protracted corticosteroid treatment (prednisolone, 5-10 mg daily) for AIH after LT and a low incidence of *r*AIH (23). Furthermore, the frequency of sepsis and osteoporosis was comparable to that encountered in the general recipient population.

Outcomes and Treatment of *r*AIH

Treatment of *r*AIH is empiric and depends on the presentation, which can be variable. When patients present with asymptomatic disease and minimal changes in liver tests or histological features, minor adjustments that increase the immunosuppression may be sufficient to suppress recurrent disease (40, 55). When patients present with severe *r*AIH, starting prednisone or prednisolone, 30 mg daily, in combination with azathioprine, 1-2 mg/kg daily, is usually effective in inducing laboratory improvement. The dose of

prednisone or prednisolone can then be reduced to 5-10 mg daily within 4 to 8 weeks and maintained thereafter (56). Failure of *r*AIH to respond to the combination of corticosteroids and azathioprine justifies consideration of other strategies, such as an alternative calcineurin inhibitor, mycophenolate mofetil (MMF), or rapamycin (57, 58).

Re-transplantation may be necessary for patients with *r*AIH who present with liver failure and graft loss. Re-transplantation has been reported mainly in children and young adults. In one North American center, 60% of children with *r*AIH developed cirrhosis, and evidence for *r*AIH was observed in all patients that required re-transplantation (41). In adults, graft failure has been reported in 13% to 50% with *r*AIH (42, 52). These reports suggest that the development of cirrhosis with subsequent graft loss occurs despite intensive immunosuppressive therapy in some patients with *r*AIH. *r*AIH has been associated with a higher risk of graft loss and an increased risk of death from liver failure compared to other liver diseases 1-year post-LT (59).

De Novo Autoimmune Hepatitis

Frequency of De novo AIH

De novo AIH is a clinical entity resembling AIH that develops in recipients transplanted for liver diseases other than AIH. It was originally described in children after LT, predominantly in those with biliary atresia (11), and subsequently found in a higher prevalence of LT recipients with PBC (12). The first description of *de novo* AIH in children in 1998 involved seven of 180 children who were followed for at least 5 years after LT. These patients presented with histological features of AIH, hypergammaglobulinemia and high titers of ANA, and/or SMA and/or anti-LKM1. Six of the seven patients responded to therapy with corticosteroids and azathioprine (11). *De novo* AIH was subsequently described

in another population of children in 2001 (60), in adults transplanted for PBC in 1999-2010 (61, 62), in adults transplanted for drug-induced liver failure, alcoholic cirrhosis, primary sclerosing cholangitis (PSC), PBC, cryptogenic cirrhosis, and hepatitis C-related cirrhosis in 2001 (63), and in 4 of 9 patients transplanted for chronic hepatitis C who had been treated with pegylated interferon (Peg-IFN) and ribavirin (RBV) for recurrent chronic hepatitis C in 2007 (64).

The term, *de novo* AIH, has been challenged, and the Banff working group on liver allograft pathology has suggested that this term be abandoned. The term, "plasma-cell rich rejection" has been recommended as a substitute since the histological features of lymphocytic cholangitis, central perivenulitis, and T cell-mediated rejection are atypical for AIH (65). Countering this proposal are observations that less potent immunosuppression appears protective against *de novo* AIH; patients with AIH can manifest these same atypical features outside the context of LT; and the majority of patients with *de novo* AIH have high serum levels of IgG and characteristic autoantibodies (3, 12, 66). Further studies will be required to determine if this form of graft dysfunction constitutes an autoimmune (*de novo* AIH) or an alloimmune (plasma-cell rich rejection) reaction (38, 67).

The frequency of *de novo* AIH has been estimated at 5-10% of pediatric recipients and 1-2% in adult recipients. In one study, *de novo* AIH was diagnosed in 17 of 576 patients (3%), and the overall incidence was 4.0 cases per 1000 patient-years (12) (Table 4).

Diagnostic Features of De novo AIH (Table 2)

The clinical manifestations of *de novo* AIH are similar to those of *r*AIH and classical AIH. Most patients have hypergammaglobulinemia, increased serum IgG levels, and ANA, SMA, or both ANA and SMA. Children with *de novo* AIH may have anti-LKM1, antibodies to gastric parietal cells, or anti-LC (68). The diagnosis has been made in the absence of autoantibodies and increased serum IgG level in some patients by depending on the

histological findings and response to immunosuppressive therapy (69, 70). An atypical anti-liver/kidney cytosolic antibody that reacts to rat hepatocyte cytoplasm, mainly in the centrilobular area, has been described in adults with *de novo* AIH, and the target antigen is glutathione-S-transferase T1 (GSTT1) (31, 71).

Portal and periportal (interface) hepatitis with lymphocytes and plasma cells are the main histological features of *de novo* AIH (11). Perivenular cell necrosis (11), lobular hepatitis (31), portal fibrosis (60, 68), zonal necrosis (61), and centrilobular necrosis (62) have also been described.

Risk Factors for De Novo AIH (Table 3)

Recipients of female grafts or older donors have a higher prevalence of *de novo* AIH, suggesting that the risk for *de novo* disease is harbored within the allograft (12). *De novo* AIH has also been related to atypical serum autoantibodies, the majority of which are directed against GSTT1 (anti-GSTT1) (72, 73). Indeed, the mismatching of donor and recipient for the GSTT1 genotype has been proposed as essential for the appearance of anti-GSTT1 and the development of *de novo* AIH (Table 3).

In one study of 419 adult recipients with donor/recipient GSTT1 mismatching, 29 patients (7%) had anti-GSTT1, and 20 of 27 assessable patients (74%) developed *de novo* AIH over a median follow-up time of 26 months. The probability of *de novo* AIH was 60% at 36 months. Multivariate analysis has identified male donor [hazard ratio (HR), 3.3; 95% CI, 1.18-9.26; P=0.02], nonalcoholic etiology (HR, 4.67; 95% CI, 1.64-13.3; p=0.002), and high anti-GSTT1 titer (HR, 2.98; 95% CI, 1.04-8.57; p=0.04) as independent predictors of *de novo* AIH (73).

Interestingly, the administration of granulocyte colony-stimulating factor (GCSF) for the treatment of neutropenia appeared to protect against *de novo* AIH in one cohort, whereas the use of anti-lymphocyte antibodies was associated with a higher risk of *de novo* AIH in

another cohort (64). Recipients treated with tacrolimus or MMF have also had a high risk of developing *de novo* AIH, whereas recipients treated with cyclosporine have had a reduced risk (12). These observations suggest that the immune mechanisms contributing to the development of *de novo* AIH are variably affected by regimens of immunosuppression that may differ by dose or combination with corticosteroids. This speculation is supported by the observation that recurrent PBC (*r*PBC) is less frequent in recipients receiving cyclosporine (6).

Outcomes and Treatment of De Novo AIH

De novo AIH can be an aggressive disease in children. In one pediatric cohort, progression to advanced fibrosis occurred in 80% of recipients, and graft loss occurred in 33% despite treatment with corticosteroids and azathioprine (60). Adult patients who develop *de novo* AIH after interferon treatment for recurrent HCV infection may also have an aggressive form of the disease. In one series, two of nine patients died, one had graft failure, and one required re-transplantation despite the rapid institution of corticosteroid treatment (64).

In one large series of patients with *de novo* AIH, 38 patients received regimens that included azathioprine, 6-mercaptopurine, prednisone, methyl prednisolone, MMF or a calcineurin inhibitor. The agents were administered alone or in various combinations, and appropriate response and acceptable outcomes were observed in only 40% of patients. Of the remaining patients, 10 died, three underwent re-LT, and 10 developed cirrhosis (74).

Prednisone or prednisolone remains the main treatment of *de novo* AIH, but combined therapy with other immunosuppressive agents has also been used. In adults, prednisone or prednisolone, 30 mg daily, in conjunction with azathioprine, 1 to 2 mg/kg daily, is recommended (56). In children, prednisone or prednisolone, 1-2 mg/kg (without surpassing 60 mg daily), in combination with azathioprine, 1-2 mg/kg, is recommended (56). The dose

of prednisone or prednisolone should be decreased during a period of 4 to 8 weeks to maintain a dose of 5-10 mg daily (56). The importance of prednisone (or prednisolone) and low dose maintenance therapy is supported by one study demonstrating that progression to cirrhosis, need of LT, or death occurred only in those patients who had not received such treatment (31).

Current and Future Strategies to Improve the Management of rAIH and De Novo AIH

It is important to emphasize that the evidence for the treatment regimens that have been used in *r*AIH and *de novo* AIH are derived from old studies and are based on small, single-center experiences using mainly standard regimens for the treatment of classical AIH. MMF has been proposed as a safe and effective first-line therapy in treatment-naive patients with classical AIH (75), and MMF may emerge as a substitute for azathioprine after LT.

Prospective multi-centric studies for the validation and improvement of diagnostic and management strategies are necessary to improve graft and patient outcomes after LT. In this regard, an important step will be to standardized criteria among the LT centers (Table 2).

The effect of induction and maintenance immunosuppressive treatment after LT on the incidence and outcomes of *r*AIH and *de novo* AIH post-LT should be assessed in a standardized manner. Future studies should also include newer immunosuppressive agents and combinations. Due to the small number of patients with *r*AIH and *de novo* AIH, this can only be achieved in a multicentric framework and with a standardized approach regarding diagnostic and treatment. Disease-specific biomarkers and a better understanding of the immunological pathomechanisms will further improve the diagnosis and management of these challenging disorders.

CONCLUSIONS

Liver transplantation for decompensated AIH is associated with 1- and 5-year survivals of approximately 90% and 70%, respectively. Recurrent disease has been reported to occur in 10-50% of recipients, and the early detection of *r*AIH by the use of protocol liver biopsies might improve detection, strengthen estimates of frequency, facilitate early intervention, and improve outcomes.

Recurrent disease can negatively influence graft and patient survival, and randomized controlled trials are warranted to assess predisposing factors and management strategies. The administration of low dose maintenance corticosteroids has been reported to minimize the occurrence of *r*AIH (23), and better control of disease activity prior to LT may lower the risk of *r*AIH (5). These strategies should be evaluated in multi-centered collaborative studies.

De novo AIH can develop in children and adults after LT for liver diseases other than AIH, and it may also result in graft failure and the need for repeat LT. Its place within the spectrum of allograft dysfunction is still uncertain, and further studies are needed to standardized its diagnosis and distinguish it from plasma cell-rich rejection. Disease-specific serological markers should be sought, and the value of testing for anti-GSTT1 determined.

Early diagnosis and prompt institution of therapy with prednisone or prednisolone in combination with azathioprine are mainstay management principles for *r*AIH and *de novo* AIH.

Authorship Statement:

- Guarantor of the article: Aldo J. Montano-Loza, MD, PhD.

- Specific author contributions:

Guido Stirnimann, search and selection of abstracts, review of full-length articles selected, and writing final version of manuscript.

Maryam Ebadi, search and selection of abstracts, review of full-length articles selected, writing final version of manuscript; and submitting manuscript for review.

Albert J. Czaja, search and selection of abstracts, review of full-length articles selected, and writing final version of manuscript.

Aldo J. Montano-Loza, search and selection of abstracts, review of full-length articles selected, creation of the first draft of the manuscript, and writing final version of manuscript.

- All authors approved the final version of the manuscript.

TABLES

Table 1: Studies Presenting Survival and Frequency of Autoimmune Hepatitis Recurrence After Liver Transplantation

Author/ Year/ Country	***n***	**Follow-up (Post-LT)**	**Frequency of *r*AIH *n* (%)**	**Time to development of *r*AIH**	**Probability of *r*AIH (%)**	**Post-LT biopsy procedure**	**Immunosuppression regimens**	**Overall Survival/Graft Survival**
Prados, et al.(40) (1998) Spain	27	3.7±2.3years (range: 8 months to 9 years) Longer follow-up in patients with recurrence than in patients without (5.1±1.9 *vs.* 2.5±1.6 years; P=0.001)	9 (33)	2.6 ± 1.5 years	8% at 1-year 68% at 5-years	Protocol biopsies (in most centres)	• *r*AIH Single therapy, n=3 (Cyclosporine or Tacrolimus) Double, n=6 (Cyclosporine + Prednisone)* • No *r*AIH Single, n=3 (Cyclosporine or Tacrolimus) Double, n=8* (Cyclosporine + Prednisone) Triple, n=7 (Cyclosporine or Tacrolimus + Prednisone + Azathioprine)	Mean post-recurrence follow-up of 2.4±1 years No difference in patient and graft survival rates post-LT between patients with and without recurrence
Milkiewicz, et al. (52) (1999) UK	47	Median follow-up of 50 months	13 (28)	29 months (range, 6–63)	NA	Protocol biopsies	Not available	Graft Loss in patients with recurrence (n=3)
Reich et al.(42) (2000) USA	32 (24 chronic AIH, 8 (sub)-fulminant AIH)	27±14 months	6 out of 24 (25)	15±2 months (range, 12-18)	NA	Clinically indicated	• *r*AIH Double, n=3 (Tacrolimus+ Prednisone) Triple, n=3 (Tacrolimus+ Prednisone+ Cyclophosphamide) • No *r*AIH	Mean post-recurrence follow-up of 23±16 months (range, 2 days to 52 months) 81% survival rate

							Not available	at 1 and 2 years post-LT Graft loss (n=3), and death (n=8) in patients with recurrence
Gonzalez-Koch, et al. (27) (2001) USA	41	Follow-up Time tended to be longer in the patients with recurrent disease (9.5±1.6 *vs.* 6.3±0.7 years; P=0.07)	7 (17)	4.6±1 years (range, 1.2 to 7.9 years)	NA	Protocol biopsies	• *r*AIH Single Tacrolimus or Cyclosporine, n=3 Triple Tacrolimus + Prednisone + Azathioprine, n=1 Cyclosporine + Prednisone + Azathioprine, n=3 Prednisone withdrawal, n=1 • No *r*AIH Single Tacrolimus or Cyclosporine, n=4 Triple Tacrolimus + Prednisone + Azathioprine, n=10 Cyclosporine + Prednisone + Azathioprine, n=20 Prednisone withdrawal, n=1	No difference in 5-year patient (86% *vs*. 82%; P=0.9) and graft (86% *vs*. 67%; P=0.5) survival between patients with and without recurrence Graft Loss (n=1) in patients with recurrence
Duclos-Valle, et al. (43) (2003) France	17	Followed for more than 10 years	7 (41)	2.5±1.7 years (range, 0.6–3.0)	NA	Protocol biopsies (n=4) Abnormal LFT (n=3)	• *r*AIH Double Cyclosporine +Prednisone, n=1	NA

							Triple Cyclosporine + Prednisone+ Azathioprine, n=6	
Montano-Loza, et al.(5) (2009) Canada	46	79±10 months (range, 6-287 months; median, 51 months)	11 (24)	48±16 months (range, 9-144 months; median, 30 months)	18% at 5 years 32% at 10 years	Clinically indicated	• *r*AIH Tacrolimus, n=7 Cyclosporine, n=4 Prednisone after LT, n=10 Long-term prednisone, n=6 Mycophenolate mofetil, n=9 Sirolimus, n=2 • No *r*AIH Tacrolimus, n=23 Cyclosporine, n=12 Prednisone after LT, n=29 Long-term prednisone, n=14 Mycophenolate mofetil, n=25 Sirolimus, n=8	Graft dysfunction after LT was 3.6 cases per 100 patient years The 5-year probability of survival in patients with and without recurrence was 82% and 76%.
Krishnamoorthy, et al. (23) (2016) UK	73	Median follow-up of 94 months (interquartile range, 55-144)	5 (7)	47± 29 months	0%, 4%, 6%, and 11% at 1, 3, 5, and 10 years	Protocol biopsies in 50% (until 2006)	• *r*AIH Triple Tacrolimus + Prednisolone + Mycophenolate mofetil, n=2 Tacrolimus + Prednisolone + Azathioprine, n=3 • No *r*AIH Single Tacrolimus, n=2 Prednisolone, n=1 Double Tacrolimus + prednisolone, n=12	Overall survival was 92%, 90%, 86%, and 73%, and regraft-free survival was 86%, 81%, 78%, and 64% at 1, 3, 5, and 10 years, respectively

							Tacrolimus + Mycophenolate mofetil, n=4 Tacrolimus + azathioprine, n=3 Cyclosporine + Prednisolone, n=2 Tacrolimus + Hydrocortisone, n=1 Triple Tacrolimus + Prednisolone + Mycophenolate mofetil, n=23 Tacrolimus + Prednisolone + Azathioprine, n=13 Tacrolimus + Prednisolone + Sirolimus, n=3 Excluded: 4 patients (died within 3 months)	

*r*AIH= recurrent autoimmune hepatitis; HLA= human leukocyte antigen; NA=not available; LT=liver transplantation; LFT=liver function tests; * data not available for all patients

Table 2: Diagnostic Criteria for Recurrence and *De Novo* Autoimmune Hepatitis

Disease	Diagnostic criteria
Recurrent autoimmune hepatitis	*Clinical criteria* - History of liver transplantation related to AIH *Serologic findings* - Hypergammaglobulinemia, increased serum IgG levels, and ANA, SMA, or both ANA and SMA (5, 23) *Histological aspects** - Prominent lymphocytic interface activity with or without plasma cell infiltration (37, 46) - Acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells (37, 46) - Pseudo-rosetting of hepatocytes, and perivenular lymphoplasmacytic inflammation (37) - Confluent and bridging necrosis with lymphoplasmacytic infiltration (severe inflammatory activity) * Features may be less pronounced, absent, or otherwise atypical in part because of concurrent antirejection therapy (43-45).
De novo Autoimmune hepatitis	*Clinical criteria* - History of liver transplantation not related to AIH *Serologic findings* - Hypergammaglobulinemia, increased serum IgG levels, and ANA, SMA, or both ANA and SMA (12) - Atypical anti-liver/kidney cytosolic antibody targeting the antigen glutathione-S-transferase T1 (GSTT1) (31, 71) - Children with *de novo* AIH may have anti-LKM1, antibodies to gastric parietal cells, or anti-LC (68) *Histological aspects* - Portal and periportal (interface) hepatitis with lymphocytes and plasma cells (11) - Perivenular cell necrosis (11), lobular hepatitis (31), portal fibrosis

	(60, 68), zonal necrosis (61), and centrilobular necrosis (62)
Recurrent and *De novo* Autoimmune hepatitis	*Exclusion of alternative etiologies* - T-cell mediated rejection: focal lymphocytic cholangitis and perivenular hepatocyte necrosis of the terminal hepatic venules support this diagnosis (37) - drug hepatotoxicity, *de novo* steatohepatitis, viral hepatitis, including hepatitis E

Table 3: Risk Factors for Recurrence and *De Novo* Autoimmune Hepatitis

Disease	Risk Factors for Recurrence	Statistical method applied
Recurrent autoimmune hepatitis	• Discontinuation of steroid therapy (52)	Observational Study*
	• HLA-miss matching between donor and recipient for HLA-DR3 or DR4 (43, 53, 76)	Observational Study (43, 76) Multivariate Cox analysis (53)
	• Tacrolimus based Immunosuppressive regimens (46)	Univariate analysis (Fisher's exact test)
	• HLA-DR3 or HLA-DR4 incidence in the transplant recipient (27)	Univariate analysis (Fisher's exact test)
	• Abnormal pre-LT AST, ALT, IgG (5)	Multivariate Cox analysis
	• Re-transplantation for recurrent AIH (42)	Observational Study
	• Transplantation for chronic AIH (patients transplanted for fulminant AIH seem to be protected from recurrence) (42)	Observational Study
	• Concomitant autoimmune disease (5)	Multivariate Cox analysis
	• Moderate to severe inflammatory activity or plasma cell penetration in the liver explants (5)	Multivariate Cox analysis
	• High-grade inflammation in the native liver at LT (46)	Univariate analysis (Fisher's exact test)
De novo Autoimmune hepatitis	• Anti-lymphocyte antibodies use (64)	Univariate analysis (Fisher's exact test)
	• Antiviral therapy for HCV infection with pegylated interferon and ribavirin (64)	Observational Study
	• Female grafts or older donors recipients (12)	Multivariate Cox analysis
	• Atypical serum autoantibodies such as GSTT1 donor/recipient genotype mismatch (72, 73)	Univariate analysis (Fisher's exact test) (72) Multivariate Cox analysis (73)
	• Tacrolimus, or mycophenolate mofetil use as part of immunosuppressive therapy (12)	Multivariate Cox analysis
	• Number of episodes of rejection (77)	Univariate analysis (Student's t-test)
	• Acute rejection episode (78)	Multivariate Cox analysis
	• Nonalcoholic etiology (73)	Multivariate Cox analysis

AIH= autoimmune hepatitis; ALT=; alanine aminotransferase; AST= Aspartate transaminase; GSTT1= glutathione S-transferase T1; HLA= human leukocyte antigen; IgG= immunoglobulin G; LT=liver transplantation;
*Observational Study: No statistical analysis was conducted

Table 4: Studies Presenting Frequency of *De Novo* Autoimmune Hepatitis

Author/ Year/ Country	*n*	Follow-up (Post-LT)	Frequency of Recurrence *n* (%)	Time to development of Recurrence	Overall Survival/Graft Survival
Pediatric Population					
Kerkar, et al.(11) (1998) UK	180	NA	7(4)	23±15 months (6-45)	Graft Loss (n=7)
Gupta, et al.(60) (2001) USA	115		6 (5)	8.5 years (range 5–13)	Graft Loss (n=1)
Spada, et al. (79) (2001) Italy	116	NA	5 (4)	29 months (range 17 to 111)	Graft Loss (n=1)
Venick, et al.(77) (2007) USA	619	NA	41(7)	7.0±1.2 years	Mean follow-up of 4 years Graft Loss (n=3) Death (n=2)
Cho, et al.(69) (2011) Korea	149	NA	4 (3)	Median of 6.5 years (range, 0.7–8.8 years)	NA
Ekong, et al. (80) (2017) USA/ Canada/ UK	1833	NA	31 (2)	Median 5.3 years (range 1.2-14.9)	Median follow-up of 7.1 years (1.6-15) Graft loss (n=2) Death (n=1)
Pediatric and Adult Population					
Miyagawa-Hayashino, et al. (78) (2004) Japan	633	6.1 (4.3–10.4) years	13 (2)	3.6±2.6 years	Patients were followed for a median of 3.5 (0.1–8) years Graft Loss (n=3)
Montano-Loza, et al.(12) (2012) Canada	576		17 (3)	84±16 months (range 3–201)	Similar survival in patients who developed de novo AIH compared to the rest of LT recipients The 5-year probability of survival was 100 and 84%

					in patients with and without *de novo* AIH
Adult Population					
Eguchi, et al.(81) (2008) Japan	72	Median follow up of 42.5 months (range 26–57 months)	4 (6)	19±19 months (range 3-41)	NA
Salcedo, et al. (73) (2009) Spain	419	Median follow up of 90.85 months (95% CI, 40.71-141.00)	20 (5)	Median follow-up of 26 months (95% CI, 19.2-32.8)	Graft loss (n=6)

HLA= human leukocyte antigen; NA=not available.

FIGURE LEGEND

Figure 1. Main pathogenic mechanisms implicated in the development of recurrent and *de novo* autoimmune hepatitis. In recurrent autoimmune hepatitis (upper row), antigen presenting cells **(**APC) of the recipient re-populate the donor liver, present self-antigens, and sensitize naïve $CD4^+$ T lymphocytes to the antigens (panel a). Self-tolerance is overridden by molecular mimicry and the targeting of homologous antigens by activated cytotoxic T lymphocytes (CTL). The mimicries may involve cytochrome P450 2D6 (CYP2D6,), transfer ribonucleic acid (tRNA); transfer ribonucleoprotein involved in serine (ser) and selenocysteine (sec) metabolism (tRNA(SER)SEC), and formiminotransferase cyclodeaminase (FTCD) (panel b). Activated $CD4^+$ T cells differentiate along cytokine pathways to activated CTL (type 1 cytokine pathway) and to B cells and plasma cells (type 2 cytokine pathway) (panel c). Antibody-producing plasma cells and activated CTL initiate an apoptotic pathway mediated by the first apoptosis signal receptor (Fas) and Fas ligand (FasL), and natural killer T (NKT) cells interact with

Fc receptors (FcR) to initiate cell-mediated cytotoxicity. The consequence of these interactions is an anti-graft response (panel d).

In *de novo* autoimmune hepatitis (second row), the APCs of the recipient re-populate the donor liver and present self-antigens (panel a). The donor CD4+ T helper cells are primed by mimics of alloantigens, glutathione-S-transferase T1 (GSTT1), antigens of the major histocompatibility complex (MHC), or viral antigens (panel b). Activated CD4+ T cells differentiate along cytokine pathways into plasma cells and activated CTL (panel c). Antibody-producing plasma cells, activated CTL, and NKT cells induce an anti-graft response (panel d).

*NKT cell CD94 (NKG2D) receptors bind to HLA class I MICA and MICB ligands and to non-HLA ULPB stress proteins expressed on target cells.

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Figure 1. Recurrent Autoimmune Hepatitis

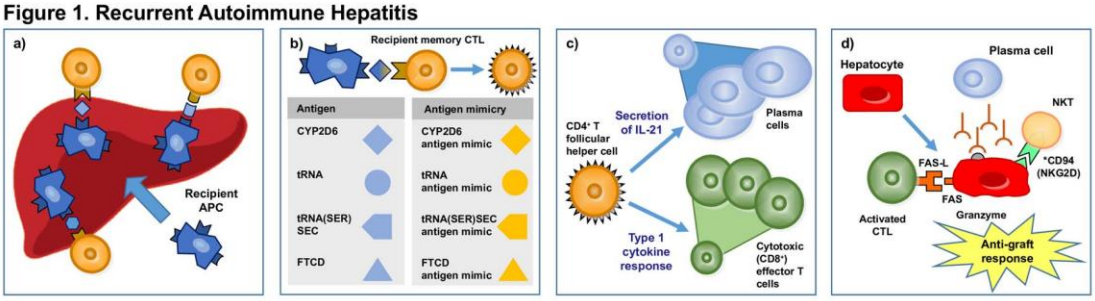

Figure 2. *De Novo* Autoimmune Hepatitis